Efficacy and Safety of the MC4R Agonist Setmelanotide in LEPR Deficiency Obesity: A Phase 3 Trial

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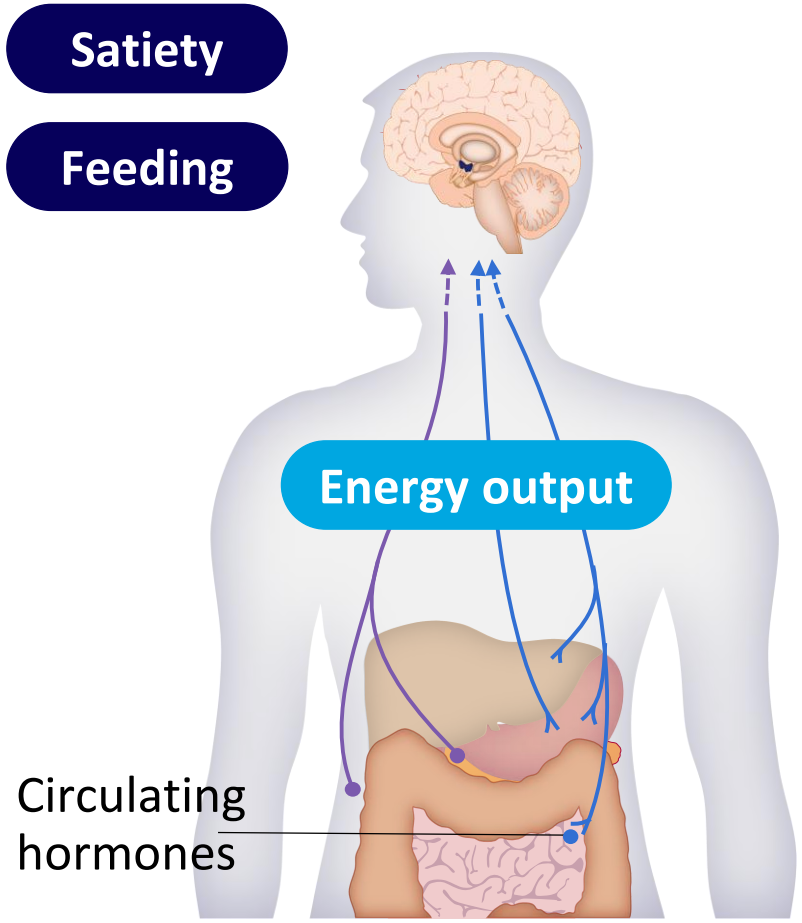
The Regulation of Body Weight Is Complex



Body weight is determined by the balance between food intake and energy expenditure[1]

The hypothalamus regulates both aspects in response to cues from peripheral hormones that reflect nutritional state[1,2]

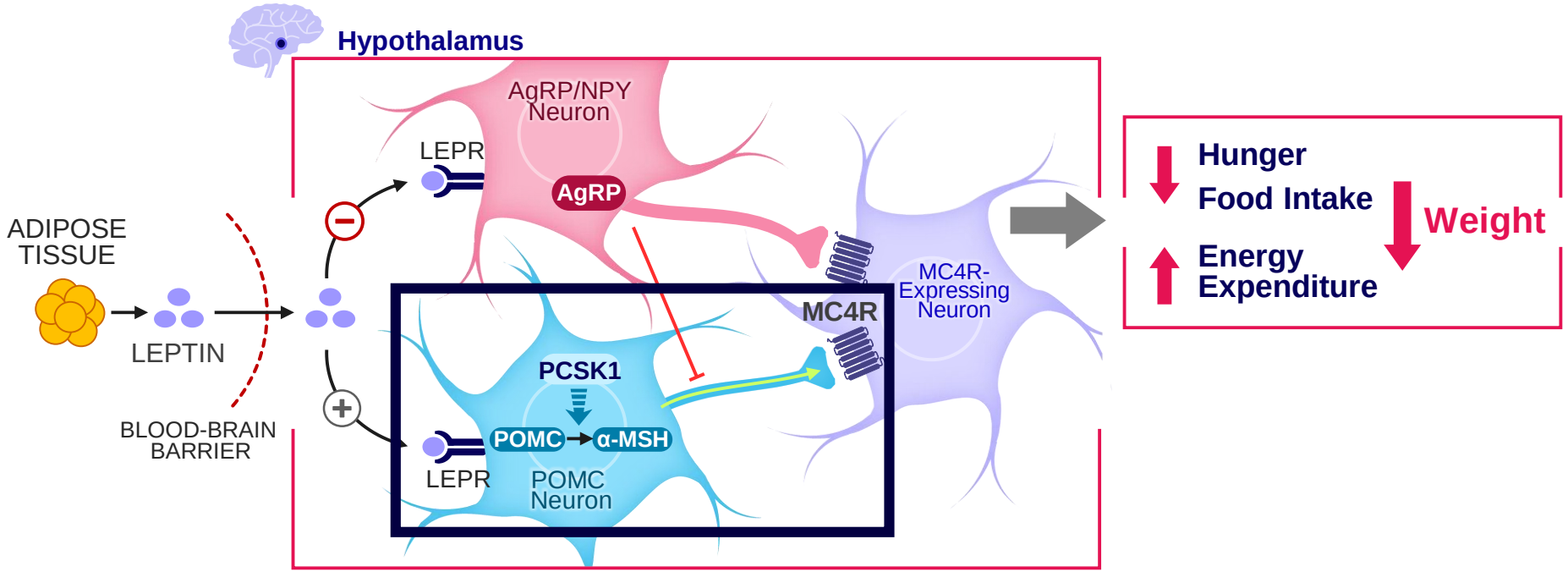
BMI, body mass index.

1. van der Klaauw and Farooqi. *Cell*. 2015;161:119-132. **2.** Cummings et al. *Diabetes*. 2001;50:1714-1719.

Figure adapted from Morton et al. *Nat Rev Neurosci*. 2014;15:367-378.

Leptin-Melanocortin Signaling Is Crucial for Regulation of Body Weight

- The melanocortin 4 receptor (MC4R) is a component of the central melanocortin pathway in the hypothalamus and is a key regulator of energy intake, expenditure, and body weight[1,2]
- Leptin is a satiety hormone that binds to leptin receptors (LEPR), resulting in MC4R-mediated reduction in food intake[1]
- Genetic variants in *LEPR* are rare and present with early-onset severe obesity and hyperphagia[1,3]

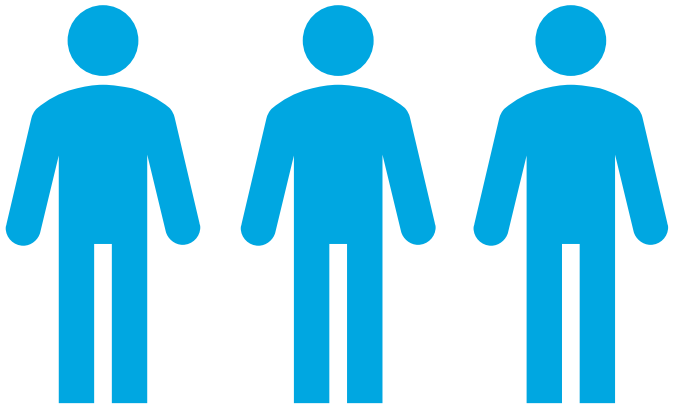


ACTH, adrenocorticotropic hormone; AgRP, agouti-related protein; LEPR, leptin receptor; MC4R, melanocortin 4 receptor; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

1. Yazdi et al. *PeerJ*. 2015;3:e856. **2.** Shen et al. *Biochim Biophys Acta Mol Basis Dis*. 2017;1863:2477-2485. **3.** Farooqi and O'Rahilly. *J Endocrinol*. 2014;223:T63-T70.

Setmelanotide Is an MC4R Agonist That Targets the Impaired Central Melanocortin Pathway

Results from a phase 2 trial showed that setmelanotide, an MC4R peptide agonist, reduced weight in 3 patients with LEPR deficiency obesity[1]

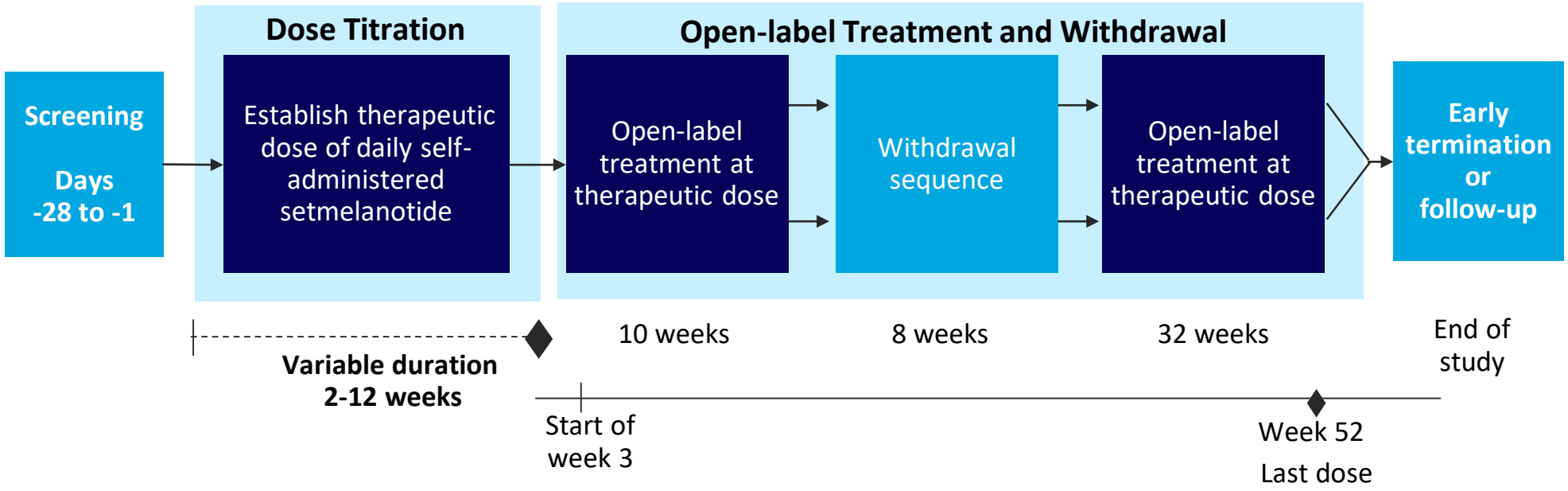


This multicenter, placebo-controlled, phase 3 trial investigated the efficacy and safety of setmelanotide in individuals with LEPR deficiency obesity

LEPR, leptin receptor; MC4R, melanocortin 4 receptor.

1. Clément et al. *Nat Med*. 2018;24:551-555.

Phase 3 Study Design



Primary endpoint:

- Proportion of participants who achieved ≥10% weight loss

Key secondary endpoints:

- Mean percent change in body weight
- Mean percent change in "most hunger" score[a]
- Proportion of participants who achieved ≥25% reduction in "most hunger" score

Post hoc analysis:

- BMI Z-scores for participants aged <19 years

Participants who lost ≥5 kg weight (or ≥5% if <100 kg) in the first open-label active treatment phase entered an 8-week, placebo-controlled phase, inclusive of a 4-week placebo withdrawal period

BMI, body mass index.

[a]"Most hunger" score was determined on a 0 to 10 Likert scale from the question, "In the last 24 hours, how hungry did you feel when you were the most hungry?"

Enrollment Criteria

Key Inclusion Criteria

- Biallelic for loss-of-function *LEPR* variants (homozygote or compound heterozygote)
- Adults (aged ≥18 years) with BMI of ≥30 kg/m^2
- Children or adolescents (aged ≥6 years to <18 years) with weight of >97th percentile for age

Key Exclusion Criteria

- Recent diet and/or exercise regimen resulting in weight loss or stabilization
- Prior gastric bypass surgery resulting in >10% weight loss with no evidence of weight regain
- Psychiatric or medical issues that would confound study results

BMI, body mass index; LEPR, leptin receptor.

Eleven Participants With LEPR Deficiency Obesity Were Enrolled

Baseline characteristics (n=11)	
Age, mean (range), years	23.4 (12-37)
Male, n (%)	3 (27)
Genotype, n (%)	
Compound heterozygous	6 (55)
Homozygous	5 (45)
Ethnicity, n (%)	
White	10 (91)
South Asian	1 (9)
Weight, mean (range), kg	133.3 (89.4-170.4)
BMI, mean (range), kg/m^2	48.2 (35.8-64.6)
"Most hunger" score, mean (range)[a]	7.1 (5-8)

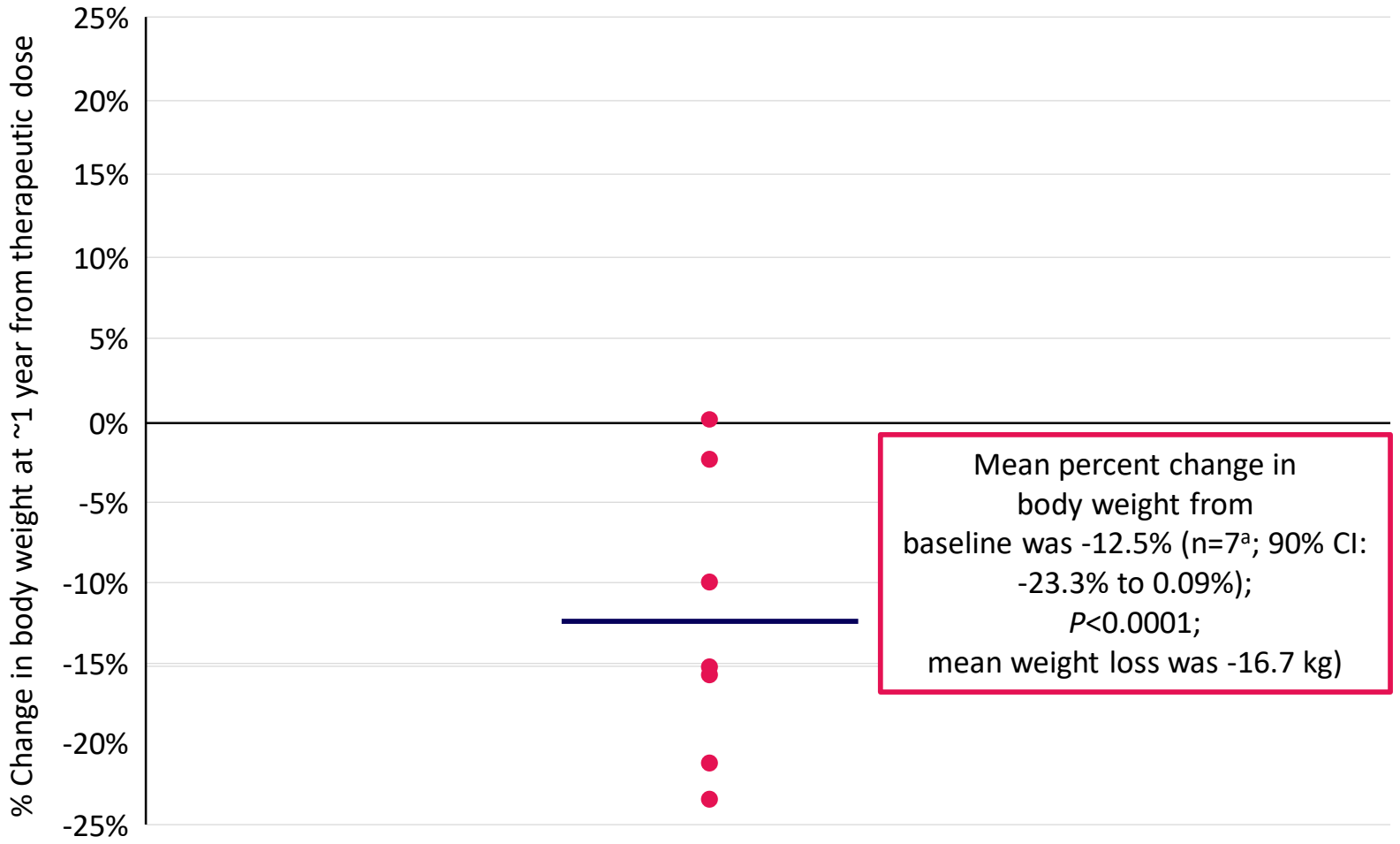
9 participants completed the trial; 2 participants discontinued

BMI, body mass index; LEPR, leptin receptor.

[a]"Most hunger" score was determined on a 0 to 10 Likert scale from the question, "In the last 24 hours, how hungry did you feel when you were the most hungry?"

Setmelanotide Was Associated With Significant Weight Reductions Over ~1 Year at Therapeutic Dose

5 of 11 participants (45%; 90% CI: 19.96% to 72.88%); *P*=0.0001) achieved the primary endpoint threshold of ≥10% weight loss from baseline



Population includes imputed data based on linear mixed effect model from n=1 participant who died from a car accident.
CI, confidence interval.
[a]Endpoint was analyzed on evaluable population (n=7), which included participants who achieved 5 kg (5% if <100 kg) body weight loss threshold after open-label period 1.

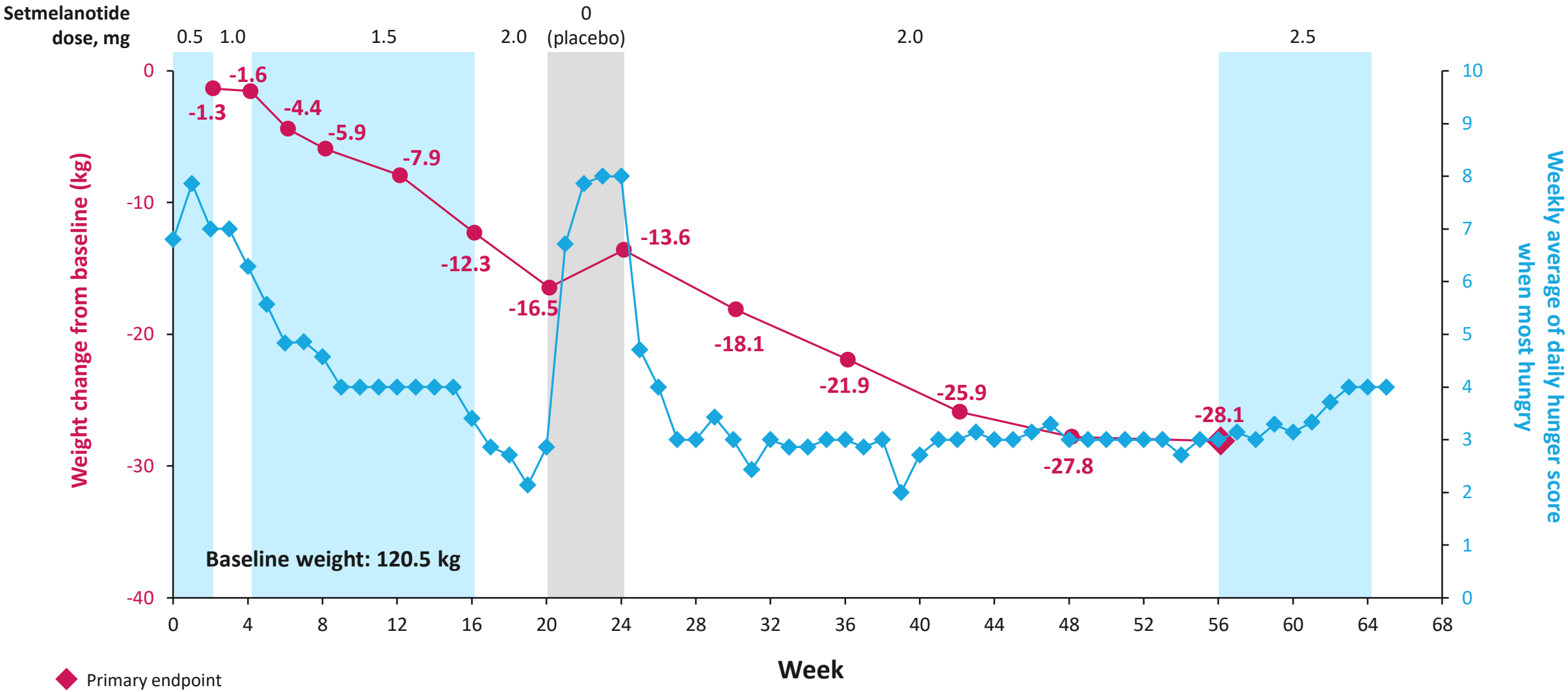
Setmelanotide Was Associated With Significant Reductions in "Most Hunger" Score Over ~1 Year at Therapeutic Dose

"Most hunger" score parameter (n=7)[a]	Mean (SD)	Range
Baseline	7.0 (0.77)	6.0 to 8.0
~1 year at therapeutic dose	4.1 (2.09)	2.0 to 8.0
Percent change from baseline, % P value	-43.7 (23.7) P<0.0001	-67.0 to 0

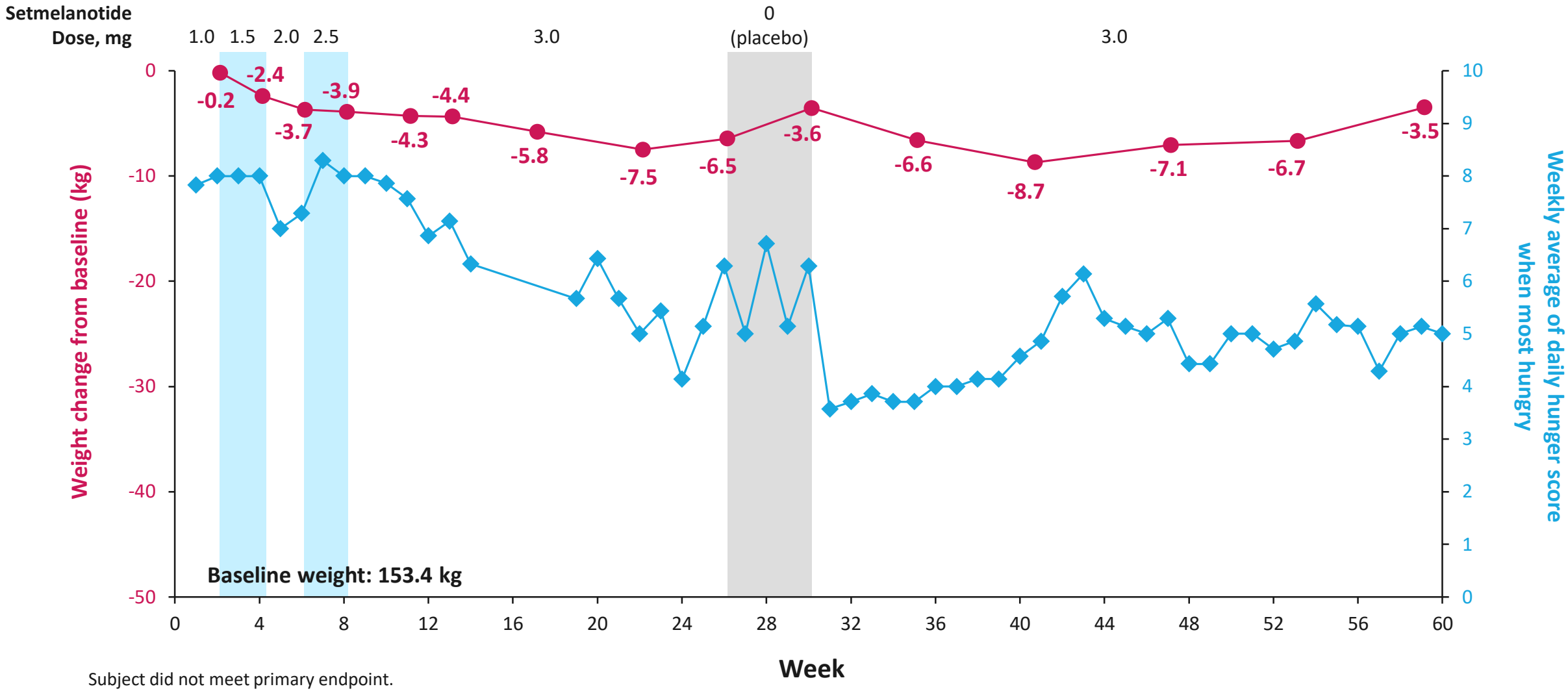
8 out of 11 participants (73%) had ≥25% reduction in "most hunger" scores from baseline (*P*<0.0001)

SD, standard deviation.
"Most hunger" score is based on 0 to 10 Likert scale from the question, "In the last 24 hours, how hungry did you feel when you were the most hungry?"
[a]Endpoint was analyzed on evaluable population (n=7), which included participants who were aged ≥12 years and who achieved 5 kg (5% if <100 kg) body weight loss threshold after open-label period 1.

Example 1 of 2 of Single Patient Body Weight and Hunger Curve Over 1 Year

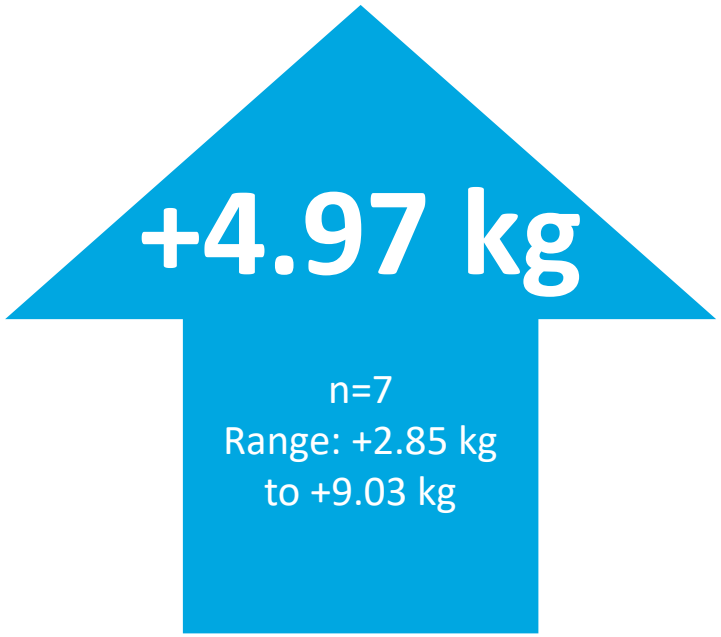


Example 2 of 2 of Single Patient Body Weight and Hunger Curve Over 1 Year



Subject did not meet primary endpoint.

Setmelanotide Withdrawal During the Placebo Sequence Was Associated With Increases in Weight and Hunger Score



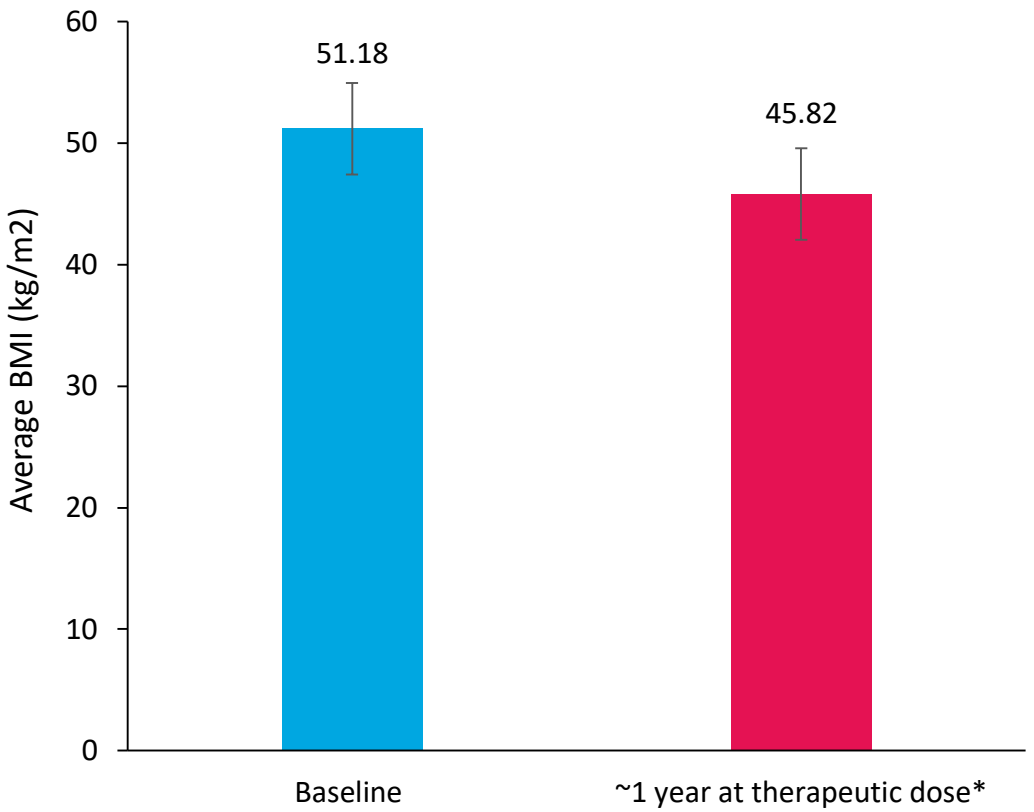
Absolute mean weight

Absolute mean "most hunger" score increase

Setmelanotide Was Associated With Reductions in BMI and BMI Z-Score Over ~1 Year at Therapeutic Dose

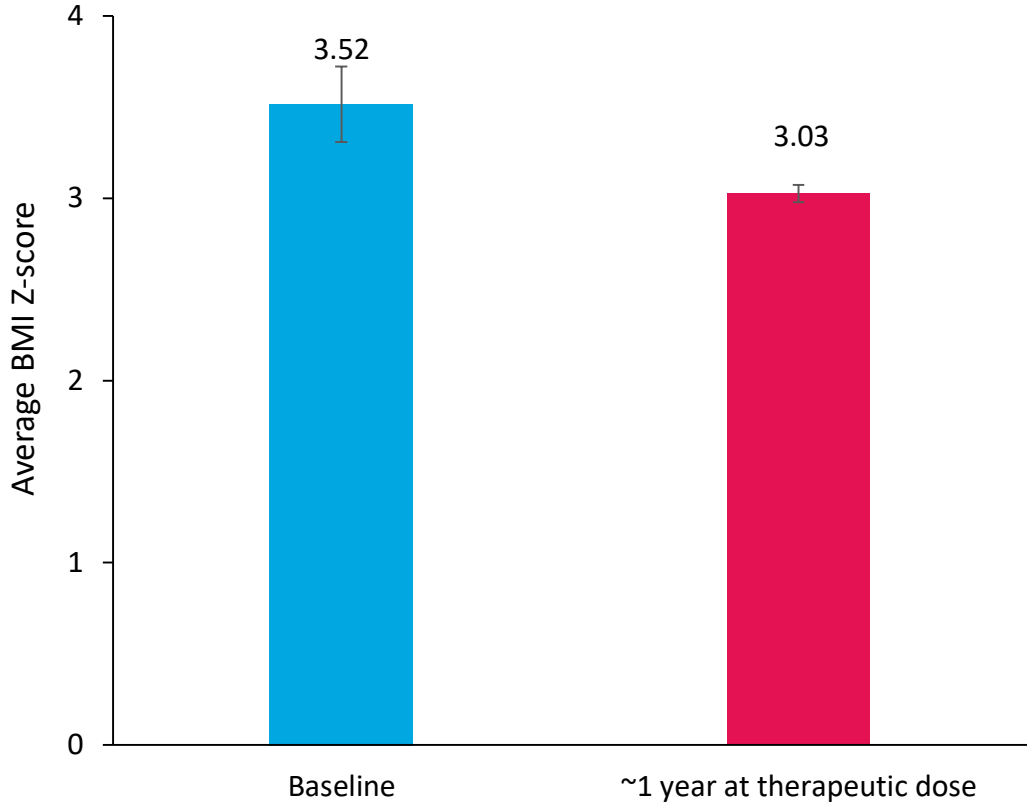
Participants aged ≥19 years (n=8)*

Mean change from baseline: -5.2 kg/m^2
Mean % change from baseline: -10.6% (P=0.01)



Participants aged <19 years (n=3)

Mean change from baseline: -0.49
Mean % change from baseline:-13.35% (P=0.012)



BMI, body mass index. *One participant was not included in the ~1 year measurement due to discontinuation due to treatment-related adverse event.
Population includes imputed data based on linear mixed effect model from n=1 participant who died from a car accident after 26 weeks at therapeutic dose. BMI baseline analysis includes n=1 participant who withdrew from the study.
Error bars are the standard error of the mean, which was calculated by dividing the standard deviation by the square root of n.

Effect of Setmelanotide on BMI and BMI Z-score

	Baseline (SD)	~1 year at therapeutic dose (SD)	Percent change from baseline, % (SD); *P* value
BMI (kg/m^2) of participants aged ≥19 years (n=8)	51.18 (10.67)	45.82 (11.48)[a]	-10.59 (8.11) *P*=0.01
BMI Z-score of participants aged <19 years (n=3)	3.52 (0.36)	3.03 (0.08)	-13.35 (8.87) *P*=0.12

Setmelanotide was associated with a significant reduction in BMI

BMI, body mass index; SD, standard deviation.
Population includes imputed data based on linear mixed effect model from n=1 participant who died from a car accident.
[a]N=7; one participant discontinued due to treatment-related adverse event.

Setmelanotide Was Well Tolerated in Individuals With LEPR Deficiency Obesity

Parameter	n (%)
Treatment-related AEs	11 (100)
Injection-site reaction	11 (100)
Hyperpigmentation	8 (73)
Nausea	5 (45)
Serious AEs	3 (27)
Serious treatment-related AEs[a]	0
Treatment-related AEs leading to discontinuation	1 (9)
AEs leading to death[b]	1 (9)

- One participant discontinued due to mild hypereosinophilia related to setmelanotide treatment
- One participant died in a car accident (passenger), and the event was not related to treatment
- Setmelanotide was not associated with significant changes in blood pressure or heart rate
- There were no reported cardiovascular AEs related to setmelanotide

AE, adverse event; LEPR, leptin receptor. [a]Four serious AEs occurred in 3 patients, including cholecystitis, road traffic accident, suicidal ideation, and gastric banding reversal. [b]Participant died in a road traffic accident (passenger) unrelated to setmelanotide treatment.

Effect of Setmelanotide on Vital Signs

	Baseline	~1 year at therapeutic dose	Percent change from baseline, %; *P* value
Diastolic blood pressure (mmHg)	67.67 (5.83)	66.48 (8.59)	-1.58 (13.04) *P*=0.73
Systolic blood pressure (mmHg)	121.70 (8.84)	115.11 (14.57)	-3.78 (9.94) *P*=0.29
Heart rate (beats/min)	79.46 (12.60)	77.89 (16.46)	-1.32 (15.46) *P*=0.80

Setmelanotide was not associated with changes in blood pressure or heart rate

mmHg, millimeter of mercury; SD, standard deviation.
Data are shown as mean (SD) for n=9 participants.

Conclusions:
Setmelanotide Reduced Hunger and Body Weight and Was Well Tolerated in Individuals With LEPR Deficiency Obesity

- In this phase 3 study, 45% of participants achieved the primary endpoint of ≥10% weight loss from baseline at ~1 year from therapeutic dose
- Setmelanotide was associated with clinically meaningful weight loss and reduction in “most hunger” score
  - Withdrawal from setmelanotide during the placebo phase was associated with significant increases in weight and “most hunger” score
- Setmelanotide was generally well tolerated
- This study is one of two phase 3 trials supporting the potential use of setmelanotide for the treatment of early-onset severe obesity and hyperphagia
  - The second phase 3 trial supports the potential use of setmelanotide in individuals with POMC or PCSK1 deficiency obesity

PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.